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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/681,205	10/09/2003	Syozo Kobayashi	243895US0DIV	5872

22850 7590 09/29/2005

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EXAMINER

TUCKER, ZACHARY C

ART UNIT	PAPER NUMBER
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1624

DATE MAILED: 09/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No.

10/681,205

Applicant(s)

KOBAYASHI ET AL.

Examiner

Zachary C. Tucker

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 25 July 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-11, 17 and 23-26 is/are pending in the application.
- 4a) Of the above claim(s) 3, 5-8 and 11 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1, 2, 9, 10, 17 and 23-26 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☒ Certified copies of the priority documents have been received in Application No. 09/762,888.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_
- ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: \_\_\_\_\_

***Response to Amendment***

As requested by applicants in the correspondence filed 25 July 2005 (hereinafter "present amendment"), which is in reply to the Office action mailed 25 January 2005 (hereinafter "previous Office action"), claims 1, 2, 11 and 23-26 have been amended and claims 12-16 cancelled.

***Election/Restrictions***

The search was broadened in view of the present amendment, and prior art anticipating the invention was found, whereupon the search was stopped. No claim in the application has been fully searched.

Claims 3, 5-8 and 11, which do not read on the elected species (compound of Example B-54 on page 902 of the specification), remain withdrawn from consideration.

***Status of Claim Rejections - 35 USC § 112***

In the previous Office action, claims 1, 2, 4, 9, 10 and 12-17 and 23-26 were rejected under the second paragraph of 35 U.S.C. 112, for indefiniteness, on many different grounds. Pages 3-7 of the Office action explain the rejections.

In view of the present amendment, some of these rejections are overcome, some are not.

Since claims 12-16 have been cancelled, the rejection of those claims are rendered moot.

The language of claim 1, where "may have a substituent," was repeatedly recited, without any notation of what substituents are included and what are excluded, has been replaced in all occurrences with "substituted or unsubstituted." This

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amendment does not overcome the rejection, which was set forth not because it was unclear whether or not substituents were contemplated, but because *what kind* of substituents are contemplated by the phrase "substituted or unsubstituted" is not known from reading the phrase in light of the instant specification. The present language "substituted or unsubstituted" presents the same problem. When read in light of the specification, the phrase "substituted or unsubstituted" is indefinite because, as was pointed out on page 4 in the previous Office action, there is not explicit definition of the term therein. Only exemplary substituents are suggested in the specification.

Since claim 1 **remains indefinite**, and all claims depend either directly or indirectly from claim 1, all claims 2, 4, 9, 10, 17 and 23-26 **remain rejected** under 35 U.S.C. 112, second paragraph, for indefiniteness.

The additional grounds of rejection with regard to claims 23-26, however, wherein those claims were found to be indefinite in the scope of which diseases are treated, is hereby withdrawn in view of the amendment thereto.

In the previous Office action, claims 1, 2, 4, 9, 10, 17 and 24-26 were rejected under the first paragraph of 35 U.S.C. 112, for lack of enablement insofar as the solvate embodiment of the compounds was concerned.

In view of applicants' argument (paragraph bridging pages 22 and 23 of remarks accompanying the present amendment) traversing the rejection, which points up the many examples of solvates provided in the instant specification, the rejection is hereby withdrawn.

The statement made by the examiner on page 9 of the previous Office action, points (F) and (G) in the enablement rejection of the claimed solvates, was erroneous.

In the previous Office action, claims 25 and 26 (the previous Office action at page 10 incorrectly states that claims "25 and 16" are rejected, but point (A) in the rejection makes clear that it is claims 25 and 26 that are rejected) were rejected for lack of a disclosure enabling the practice of the treatment of all embolisms. Since the compounds according to the invention are antithrombotic drugs, only thromboembolic conditions are treatable with said compounds, not *all* types of embolic disorders.

In view of the amendment to claims 25 and 26, the rejection is hereby withdrawn.

***Status of Claim Rejections - 35 USC § 102***

In the previous Office action, claims 1, 2, 4, 9, 10 and 17 were rejected under 35 U.S.C. 102(e) as being anticipated by US 6,600,731 (Klimkowski et al), which claims domestic priority to provisional application 60/113,595, filed 24 December 1998.

In view of applicants' having perfected the foreign priority date of the instant application, which antedates the effective filing date of Klimkowski et al, the rejection based thereon is hereby withdrawn.

In the previous Office action, claims 1, 2, 4, 9 and 10 were rejected under 35 U.S.C. 102(b) as being anticipated by US 5,654,305 (Sheppard et al).

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In view of applicants' argument traversing the rejection, which points out that T<sup>1</sup> in claim 1 cannot be ethylene, as is the case with the reference compound, the rejection based on Sheppard et al is hereby withdrawn.

***Status of Claim Rejections - 35 USC § 103***

In the previous Office action, claims 24-26 were rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,660,739 (Klimkowski et al).

In view of the perfection of the foreign priority filing date of the instant application, Klimkowski et al is no longer prior art under 35 U.S.C. 102(e). Therefore the obviousness rejection based thereon is no longer tenable, and is hereby withdrawn.

In the previous Office action, claims 17 and 23-26 were rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,654,305 (Sheppard et al).

Because the reference compound from Sheppard et al is not embraced by the instant claims, the premise of the obviousness rejection based on Sheppard et al is false, therefore the rejection under 35 U.S.C. 103(a) based thereon is hereby withdrawn.

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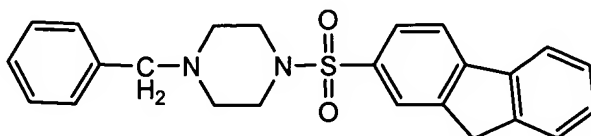
***New Claim Rejections - 35 USC § 102***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 9, 10 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by US 4,857,644 (Abou-Gharbia).

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Abou-Gharbia teaches a compound of instant claims 1, 9 and 10 in Example 2, col. 4, lines 5-32. This compound, named 1-(9*H*-fluoren-2-ylsulfonyl)-4-(phenylmethyl)piperazine hydrochloride is the hydrochloride salt of a compound having this structure –



which is embraced by the above-indicated claims wherein Q<sup>1</sup> is unsubstituted phenyl; Q<sup>2</sup> is a bond; T<sup>1</sup> is methylene; Q<sup>3</sup> is 1,4-piperazinyl; Q<sup>A</sup> is an unsaturated tricyclic group (fluorenyl).

A composition according to instant claim 17, comprising the compound of example 2 is disclosed in Abou-Gharbia, dissolved in 0.5% methylcellulose, is disclosed in Example 6, which appears in column 5. The composition was administered orally to rats.

Other types of pharmaceutical compositions are taught in column 2, lines 66-67 to column 3, lines 1-18.

Claims 1, 2, 4, 9, 10, 17, 23 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 98/21188 (Preston et al). Preston et al was cited by applicants in the Information Disclosure Statement filed 9 October 2003 (as item "AM").

On pages 39-42, compounds 1-12 are disclosed, represented with the molecular structures therefor. Each one of compounds 1-12 in Preston et al is a compound according to instant claims 1, 2, 4, 9, 10, wherein Q<sup>1</sup> phenyl substituted with pyrimidine,

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pyridazine or pyridine; Q<sup>2</sup> is a bond; T<sup>1</sup> is carbonyl; Q<sup>3</sup> is 1,4-piperazinyl; Q<sup>A</sup> is bromo-naphthyl (R<sup>18</sup> is halogen).

A pharmaceutical composition according to claim 17 is disclosed in Example "d)," which bridges pages 20-21 of Preston et al. The Factor Xa-inhibiting compounds disclosed by Preston et al were administered to rats orally, in the form of a composition.

By virtue of the *in vivo* experiments found at pages 20-21 of Preston et al, the method according to claims 23 and 24 is disclosed in Preston et al as well. Preston et al's compounds are Factor Xa inhibitors, and when administered to rats, had a measurable inhibitory effect on that enzyme, and also therefore inhibited coagulation in those animals.

### ***New Claim Rejections - 35 USC § 103***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/21188 (Preston et al).

Preston et al is applied against claim 26 as set forth above in the rejection of claims 2, 4, 9, 10, 17, 23 and 24 under 35 U.S.C. 102(b).

At the time the invention was made, the method according to claims 25 and 26 would have been obvious to one of ordinary skill in the art, given the teachings of Preston et al.

The deficiency of Preston et al with respect to instant claims 25 and 26 is that the publication does not disclose an actual treatment according to those claims, by



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administering the Factor Xa inhibitor compounds from the examples to a subject (*i.e.*, a patient) undergoing treatment for one of the conditions recited in the rejected claim.

Preston et al, however, *does* expressly suggested doing so in the paragraph bridging pages 22 and 23, specifically in points vi (treating coagulation disorders) and vii (treatment thrombosis or embolism involving Factor Xa mediated coagulation).

The motivation to treat thrombosis, recited in claim 25, or one of the more specific conditions recited in claim 26, by administering a compound disclosed in the Preston et al publication would have been to mediate the deleterious effects of those disease states.

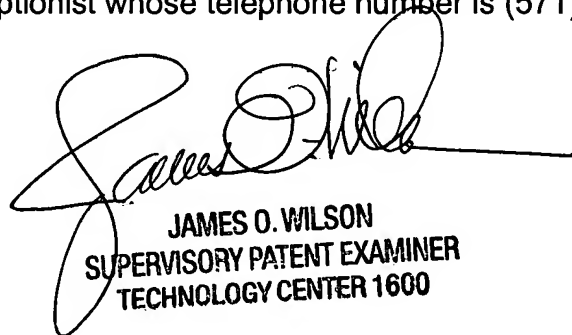
### **Conclusion**

Any inquiry concerning this communication should be directed to Zachary Tucker whose telephone number is (571) 272-0677. The examiner can normally be reached Tuesday-Thursday from 8:00am to 4:30pm or Monday from 6:00am to 1:30pm. If Attempts to reach the examiner are unsuccessful, contact the examiner's supervisor, James O. Wilson, at (571) 272-0661.

The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

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